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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/614,866	07/07/2003	Jane Hirsh	CP 100	8191

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PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE, SUITE 1200
1201 PEACHTREE STREET
ATLANTA, GA 30361

EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	**PAPER NUMBER**
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/614,866	HIRSH ET AL.	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23,26,27,29 and 33-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,26,27,29 and 33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendment, response and declaration dated 6-29-07 is acknowledged.

Claims 1-23, 26, 27, 29 and 33-40 are pending in the instant application.

The following rejection of record has been maintained:

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 2, 4-7, 9-13, 16-26 and 33-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,310,072 to Smith et al (Smith) in view of US 6,696,088 (Oshlack et al).

Smith teaches pharmaceutical compositions comprising a combination of mu and kappa opioid agonists such as morphine and oxycodone respectively. In particular, Smith teaches salts of the opioid agonists such as pectinate and terephthalate, both of which have been described in the instant application as lipophilic derivatives (col. 5, L 5-10, L 41-43). Smith suggests oral and subcutaneous methods of administering the composition, wherein the controlled release dosage forms are coated with hydrophobic polymers such as higher fatty alcohols (col. 8, L 49-63). While the reference suggests controlled release as well as immediate release of the drugs, Smith does not teach a formulation of oxycodone that is dispersed in the insoluble formulation for preventing the immediate release of the drug upon loosing its integrity.

Oshlack teaches a tamper resistant and also abuse resistant oral opioid formulation, in which the active agent is not delivered immediately (col. 5, col. 6, L 42-60

& lines bridging col. 8-9). Oshlack teaches the same active agents that are claimed and in particular oxycodone (entire col. 14 & col. 16, L 1-19) and suggests salts of the opioid compounds such as sulfates, methanesulfonate, benzenesulfonates, phosphates etc (col. 11, L 45-61), which are dispersed in a non-releasable matrix or as coated particles made of hydrophobic and water-insoluble material. The latter hydrophobic material is selected from the group consisting of ethyl cellulose, cellulose acetate phthalate, acrylic polymers, fatty acids, fatty alcohols, waxes etc (col. 27, L 25-col. 29, L 37). Preferably, Oshlack teaches hydrophobic materials such as waxes, fatty acids etc (col. 28, L18-54). Oshlack further teaches coating of the non-releasable dosage forms with materials such a shellac, zein etc (col. 23, L 2-12), which admittedly reads on the enzyme degradable coating of the instant claims. Oshlack also teaches microparticles, coated microparticles and enteric coating materials such

Thus, Oshlack is also in the same field of endeavor as that of the instant i.e., preparing abuse resistant formulations of opioid analgesics and delaying the immediate release of the drug that results in abuse of the substance.

While instant claims recite lipophilic derivatives of the drug, Oshlack teaches salts of the opioid drugs such as organic amine salts (picoline, ethanolamine, triethanolamine, dibenzyldiethyldiamine etc., (col. 11, L 45-52), which read on the instant lipophilic derivatives.

Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use the controlled release formulation i.e., the insoluble material selected from fats, fatty alcohols, waxes and insoluble cellulose polymers of

Oshlack for preparing a controlled release dosage formulation of terephthalate or pectinate salt of oxycodone because Oshlack teaches that opioid analgesics have a potential for the development of tolerance and physical dependence with repeated opioid use resulting in addiction (abuse) and that the abuse can be controlled by sequestering the bioavailability of the drug upon administration i.e., by preventing the immediate availability of the drug.

New claims 39 and 40 have been rejected under this section for the reasons explained above.

2. Claims 15 is are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,310,072 to Smith et al (Smith) in view of US 6,696,088 (Oshlack et al) as applied to claims s 2, 4-7, 9-10, 16-26 and 33-36 above, and further in view of US 6,048,736 to Kosak or US 5,756,483 to Merkus ('483, previously cited in the non-final rejection).

Smith and Oshlack, discussed above, do not teach the claimed complexes in particular the cyclodextrin complexes.

Kosak teaches cyclodextrin polymers for carrying drugs and other active agents and for controlled release of active agents. Kosak teaches that when the polymers are conjugated to the cyclodextrin molecules, the drugs can be designed solely for efficacy without regard for solubility and their targeted release. Kosak teaches employing a number of active agents with cyclodextrin including narcotics (col.3).

'483 teach compositions comprising morphine, apomorphine, ergotamine etc., compounds and their administration in combination with cyclodextrin or a

polysaccharide (abstract, examples and col. 4, lines 50-67). '483 teach that cyclodextrin and other saccharides increase the stability of the drug and thus increase their bioavailability. Therefore, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to prepare morphine and oxycodone compositions comprising cyclodextrin because both Kosak and '483 suggests that drug complexes with cyclodextrin improves the solubility and their targeted release. A skilled artisan would have expected to release the drug combination of Smith in a delayed (Oshlack) and yet targeted fashion (Kosak) so as to further improve drug abuse of the opioid drugs.

Response to Arguments

Applicant's arguments and the declaration of Dr. Fleming filed 6-29-07 have been fully considered but they are not persuasive.

U.S. Patent No. 6,310,072 to Smith

It has been argued as follows:

Smith discloses generally "dosage forms include tablets, dispersions, suspensions, injections, solutions, syrups, troches, capsules, suppositories, aerosols, transdermal patches and the like. These dosage forms may also include injecting or implanting controlled releasing devices designed specifically for this purpose or other forms of implants modified to act additionally in this fashion. Controlled release of the strong opioids may be affected by coating the same, for example, with hydrophobic polymers including acrylic resins, waxes, higher aliphatic alcohols, polylactic and polyglycolic

acids and certain cellulose derivatives such as hydroxypropylmethyl cellulose. In addition, the controlled release may be affected by using other polymer matrices, liposomes and/or microspheres."

It has been argued that there is no disclosure of incorporating or dispersing the drug first into a lipophilic or water insoluble carrier.

U.S. Patent No. 6,696,088 to Oshlack

It has been argued as follows:

Oshlack is discussed in detail and compared to the claimed formulations in the accompanying Declaration of Dr. Fleming. Oshlack describes oxycodone formulations. These are mixed with another drug to make them less desirable to abusers who are unable to separate the oxycodone from the second drug when they extract the drugs from the carrier. Oshlack discloses a formulation that prevents release of the second drug (antagonist) from the intact dosage form. This is achieved by coating the tablets with a polymer such as an acrylic resin or hydroxycellulose. This does not prevent the drug from being extracted after the tablet is crushed, however, since crushing disrupts the coating. In fact, the coating is specifically designed to release the second drug upon crushing *(see* col. 8, line 64 to col. 9, line 6).

In contrast, since the drug is incorporated in water-insoluble particles and then formulated as defined by the claims in the present application, crushing does not disrupt the coating and the abuser still has great difficulty in extracting the oxycodone.

Applicants' arguments are not persuasive because while Smith fails to teach that the drug is dispersed in insoluble formulation, Oshlack provides formulations comprising the same drug as that of Smith, prepared in several ways, such as matrix formulations (col. 27-28) employing hydrophobic materials (see col.27-28 and col. 30-31). With respect to the argument that Oshlack teaches an opioid agonist with another drug is not persuasive because instant claim language does not exclude the presence of a second drug of Oshlack. The argument that the coating taught by Oshlack is specifically designed to release the second drug is not persuasive because the reference teaches that opioid antagonist is made available but not the opioid agonist (such as oxycodone), which the reference describes as being protected from tampering (see col.9, L 15-24, col. 3, L 38-51, col. 43, l 14-18). Oshlack also teaches dispersing the opioid agonist in a hydrophobic material such as waxes, fatty materials and hence as described by Oshlack, is not available upon physical tampering. With respect to the declaration of Dr. Fleming, while instant claims recite that the composition prevents the immediate release of the drug, instant compositions (described on page 3 of the declaration) also provide immediate release of the drug up to 32%, which is a significant release. Applicants admit in the instant specification (pages 3-4) that the US patents such as US 6,309,668, US 6277384 and US 6375957 describe drug formulations comprising opioid agonist and an antagonist, which are successful in deterring abuse but has the potential to produce adverse effects in legitimate patients. In this regard, examiner notes that Oshlack reference provides the same description of the formulations as that of the above patents and accordingly, it is implicit that the compositions of Oshlack constitute abuse

deterrent. Further, Oshlack does state that the analgesic effects of opioid agonist are not affected and there is risk of precipitating withdrawal, thus suggesting no adverse effects.

Applicants argue that :

U.S. Patent No. 6,048, 736 to Kosak is similar to Oshlack in disclosing coatings that decrease extraction, but only until the tablet is crushed. *U.S. Patent No. 5, 756,483 to Merkus* teaches the nasal administration of a drug in combination with cyclodextrin (preferably methylated beta-cyclodextrin) or polysaccharide in order to improve the stability or bioavailability of the drug. The claims and specification disclose the formation of a complex between a drug and a poorly water-soluble cyclodextrin (e.g., ethylated beta-cyclodextrin) in order to achieve a lipophilic derivative of the drug (See paragraph 0040). Based on the teachings of '483, it would not have been obvious to one of ordinary skill in the art to complex a drug with a cyclodextrin in order to form a lipophilic derivative of the drug, nor to incorporate it into a water insoluble carrier to reduce extractability. None of the references disclose incorporation of a drug, especially a lipophilic drug or lipophilic drug derivative into a water insoluble or lipophilic material as claimed, or the basic concept, which is effective to reduce extractability even after crushing.

The above arguments are not persuasive because the formulation that prevents abuse has been described by Oshlack reference. Kosak and Merkus references have been cited to show cyclodextrin conjugates of active agents such as those claimed for

increased stability and targeted release. Accordingly, a skilled artisan would have been able to improve the drug solubility and release, which is also desired by the instant application (pages 11-12). Hence the rejection of record has been maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 7.00 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AU 1615
September 17, 2007

LAKSHMI S. CHANNAVAJJALA
PRIMARY EXAMINER